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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,022	11/24/1998	SILVIO DE FLORA	P8903-8035	7341

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
OWENS JR, HOWARD V	
ART UNIT	**PAPER NUMBER**
1623	43

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/125,022	Applicant(s) DE FLORA ET AL.	
	Examiner Howard V Owens	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *41* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Arguments

The following is in response to the request for reconsideration filed 4/30/03:

An action on the merits of claims 13-17 is contained herein below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 U.S.C. 102(b)

Applicant's arguments filed 4-30-03 have been fully considered but they are not persuasive.The rejection of claims 13 - 17 under 35 U.S.C. 102(b) as being anticipated by either Freeman et al. (Freeman), *Toxicology and Applied Pharmacology*, vol. 54, pp. 168-175 or Doroshow et al. (Doroshow), *J. Clinical Investigation*, vol. 68, pp. 1053 – 64 is maintained for the reasons of record set forth herein.

The claims are directed to a method for inhibiting formation of a metastasis in a patient having a primary cancerous tumor, which has not yet metastasized but is capable of metastasizing, comprising the administration of a synergistically effective amount of N-acetyl-cysteine and doxorubicin. Claim 14 specifies that the dosage of N-acetylcysteine be between 100 mg and 6g/day. Claim 15 requires that the doxorubicin be administered in an amount of between 1 and 50 mg per dose. Claims 16 and 17 are drawn to intravenous administration wherein the primary tumor capable of metastasizing is in the lung.

Freeman teaches that doxorubicin (adriamycin) is a potent anticancer agent which is useful in treatment of malignant lymphomas. Malignant is defined as "tending to produce death or deterioration; tending to infiltrate, metastasize, and terminate fatally"; therefore the use of doxorubicin to treat tumors which have not yet metastasized had been clearly set forth in the prior art (p.168). Freeman anticipates the combination of doxorubicin and N-acetylcysteine in the treatment of cancer in the dosage ranges that overlap with applicant's ranges (see table 1). Moreover, the improved

chemotherapeutic efficacy or synergism of doxorubicin when combined with N-acetylcysteine is taught by Freeman as it teaches (p.174, col.1-2), *"In fact, at the lower dose or adriamycin, the increase in life span was even greater with concurrent administration of the sulfhydryl compounds, which suggests that the adriamycin-sulfhydryl compound combination potentiates the antineoplastic effect of adriamycin".* The instant claim language is drawn to a tumor that "has not yet metastasized, but is capable of metastasizing.."; therefore, any teachings by Freeman that are drawn to the combination of doxorubicin and N-acetylcysteine to inhibit cancer growth are anticipatory; moreover, it is inherent to administer an anticancer compound to a tumor to inhibit the growth of the tumor or eradicate the tumor so that metastasis does not occur.

Doroshow anticipates the claims cited supra as it teaches the combination of n-acetylcysteine and doxorubicin in the treatment of tumors (pp. 1053-1054) within the claimed dosage range. Doroshow teaches the synergistic effect as it teaches that pretreatment with n-acetylcysteine significantly reduced long term mortality in animals receiving doses of doxorubicin and that n-acetylcysteine may provide a means to enhance the chemotherapeutic index of doxorubicin.

In response to applicant's argument that the prior art is not applicable to metastasis and that no evidence or scientific reasoning is provided to establish that the functional limitation is an inherent characteristic of the prior art. Applicant should note that the claim language is not drawn to a definite presence of metastasis, but rather "capable of metastasizing". Applicant states at the outset that "it is noted that the claims also include other limitations . In this case, the patient to whom the pharmaceutical is administered must have a primary cancerous tumor" while later stating that Freeman and Doroshow involved "primary tumors" which were incapable of determining the effect of the treatment on metastasis. Thus applicant recognizes that the teachings of Freeman and Doroshow are probative to the treatment of primary tumors, but not probative to claim language which recites the treatment of primary tumors. If the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates, *Atlas Powder*, 190 F.2d 1342, citing *In re King*,

801 F.2d 1324; 231 USPQ 136,138 (Fed. Cir. 1986). Applicant should note that the claim language is drawn to primary tumors that have not metastasized, not a method of treating metastasis. It is basic scientific reasoning that the whole goal of treating a tumor is to prevent the growth or spread of the tumor, applicant's base assertion that one of skill in the art in cancer treatment does not have this objective in mind is clearly not based in fact nor consistent with the modality employed for benign tumors versus those deemed to be malignant or metastatic. In the breadth of ancillary documents submitted, applicant provides no response to the fact that they are administering the same two agents in the same dosage range to treat the same target, a primary tumor in a patient, to which the prior art of Doroshow and Freeman is equally aimed at.

Applicant seems to ignore the basic purpose for using Doxorubicin (dox) in the art that provides a legitimate basis for the inherency of treating a primary tumor capable of metastasis, dox like all chemotherapy, is a cytotoxic medicine (routinely administered intravenously) which interferes with the ability of cancer cells to divide and reproduce. Given that metastasis is the uncontrolled growth and division of a tumor cell, the administration of dox as a cytotoxic agent in the prior art for the arrested development of primary tumors is concurrent with that of applicant's invention.

Applicant wonders how inherency can be supported when Doroshow states that the administration of doxorubicin does not interfere with the drug's antitumor activity against P388 leukemia. Applicant is therefore assuming that something that does not interfere with anticancer activity does not act positively nor synergistically. The statements in Doroshow simply demonstrate that one of skill in the art would not expect the cancer treating ability of doxorubicin to be diminished (emphasis added). As such, one of skill in the art would certainly appreciate that the use of NAC to combat the side effects of dox would allow for an increase in the dosage to treat

aggressive primary tumors while reducing the incidence of mortality from the cardiotoxic side effects of dox.

Statements about FDA approval are moot, considering that the examination or grant of a U.S. patent is not dependent upon FDA approval.

A 35 U.S.C. 102 anticipation rejection is not based on whether a practice is accepted protocol, but whether the invention was in the public domain at the time of filing as such applicant's assertion that the combination of NAC and dox was not an accepted practice, while admitting that Freeman and Doroshow demonstrate practice of the combination is contradictory and not probative to establishing whether the combination of the two agents to treat a tumor was in the public domain at the time of filing.

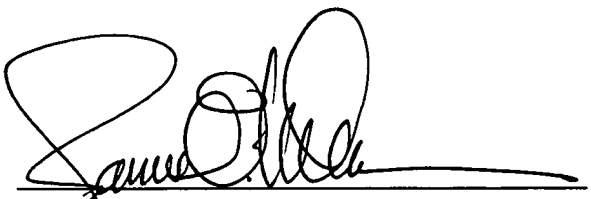
With regard to peer review recognition of applicant's invention and inherency, "Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art." ("Inherency in U.S. Patent Law", The John Marshall Law School, Center for Intellectual Property Law News Source, Vol. III, No. 1, Page 17 (Winter 2001)).

For the reasons cited above, the rejection of claims 13-17 under 35 U.S.C. 102(b) is maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Howard V. Owens
Patent Examiner
Art Unit 1623



James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Howard Owens whose telephone number is (703) 306-4538 . The examiner can normally be reached on Mon.-Fri. from 8:30 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Supervisory Patent Examiner signing this action, James O. Wilson can be reached on (703) 308-4624 . The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.